NeuroImage 172 (2018) 632–641

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

"Brain over body"–A study on the willful regulation of autonomic function during cold exposure

Otto Muzik[a,b,*], Kaice T. Reilly[c], Vaibhav A. Diwadkar[d]

[a] Departments of Pediatrics, Wayne State University School of Medicine, Detroit, MI 48201, USA
[b] Departments of Radiology, Wayne State University School of Medicine, Detroit, MI 48201, USA
[c] TKR Research and Consulting, LLC, Detroit 48201 USA
[d] Departments of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI 48201, USA

ARTICLE INFO

Keywords:
Wim Hof method
CNS thermoregulation
Cold exposure
Functional MRI
FDG PET
Hydroxyephedrine PET
Stress-induced analgesia
Periaqueductal gray

ABSTRACT

The defense of body temperature against environmental thermal challenges is a core objective of homeostatic regulation governed by the autonomic nervous system. Autonomous mechanisms of thermoregulation are only weakly affected by top-down modulation, allowing only transient tolerance for extreme cold. There is however, anecdotal evidence of a unique set of individuals known for extreme cold tolerance. Here we present a case study of a 57-year old Dutch national, Wim Hof, the so-called "Iceman", with the ability to withstand frequent prolonged periods of extreme cold exposure based on the practice of a self-developed technique involving a combination of forced breathing, cold exposure and meditation (collectively referred to as the Wim Hof Method, henceforth "WHM"). The relative contributions of the brain and the periphery that endow the Iceman with these capabilities is unknown. To investigate this, we conducted multi-modal imaging assessments of the brain and the periphery using a combination of fMRI and PET/CT imaging. Thermoregulatory defense was evoked by subjecting the Iceman (and a cohort of typical controls) to a fMRI paradigm designed to generate periods of mild hypothermia interspersed by periods of return to basal core body temperature. fMRI was acquired in two separate sessions: in a typical (passive) state and following the practice of WHM. In addition, the Iceman also underwent a whole body PET/CT imaging session using the tracers C11-hydroxyephedrine (HED) and 18F-fluorodeoxyglucose (FDG) during both thermoneutral and prolonged mild cold conditions. This acquisition allowed us to determine changes in sympathetic innervation (HED) and glucose consumption (FDG) in muscle and fat tissues in the absence of the WHM. fMRI analyses indicated that the WHM activates primary control centers for descending pain/cold stimuli modulation in the periaqueductal gray (PAG), possibly initiating a stress-induced analgesic response. In addition, the WHM also engages higher-order cortical areas (left anterior and right middle insula) that are uniquely associated with self-reflection, and which facilitate both internal focus and sustained attention in the presence of averse (e.g. cold) external stimuli. However, the activation of brown adipose tissue (BAT) was unremarkable. Finally, forceful respiration results in increased sympathetic innervation and glucose consumption in intercostal muscle, generating heat that dissipates to lung tissue and warms circulating blood in the pulmonary capillaries. Our results provide compelling evidence for the primacy of the brain (CNS) rather than the body (peripheral mechanisms) in mediating the Iceman's responses to cold exposure. They also suggest the compelling possibility that the WHM might allow practitioners to develop higher level of control over key components of the autonomous system, with implications for lifestyle interventions that might ameliorate multiple clinical syndromes.

Introduction

Defending body temperature against environmental thermal challenges is one of the most fundamental of homeostatic functions governed by the central nervous system (CNS) and has high adaptive significance. In addition to triggering thermoregulatory responses, cold exposure generates aversive feelings that mediate behavioral avoidance. This cascade of events induces avoidance that pre-empts the potentially tissue-damaging effects of cold exposure challenge. Thus, stress-induced suppression of sensitivity to external aversive stimuli is an in-built

* Corresponding author. PET Center, Children's Hospital of Michigan, 3901 Beaubien Blvd, Detroit, MI 48201, USA.
E-mail address: otto@pet.wayne.edu (O. Muzik).

https://doi.org/10.1016/j.neuroimage.2018.01.067
Received 16 June 2017; Accepted 26 January 2018
Available online 10 February 2018

mammalian mechanism that might be thought of as a component of the fight and flight response. Human biological adaptability, genetics and natural selection can all modify or mediate some of these responses (Hancock et al., 2008; Lasker, 1969; Racimo et al., 2017) but within a limited range. In general, extreme abilities to withstand cold exposure rarely emerge within the lifespan of individuals as thermoregulatory mechanisms are largely autonomous and not subject to willful and/or tonic modification (Daanen and Van Marken Lichtenbelt, 2016). Nevertheless, evidence exists of individuals with extreme and inexplicable cold tolerance significantly outside of typical limits, yet they have rarely been subjected to scientific inquiry, and never to neuroimaging.

With these issues in mind, here we present a case study of a 57-year old Dutch national, the so-called “Iceman”, who can withstand frequent prolonged periods of extreme cold exposure. This tonic capability in the Iceman appears to result from the rigorous self-application of a specially developed technique (the Wim Hof Method, WHM). The WHM consists of the daily practice of a combination of three main elements: a) initial forced breathing (several rounds of hyperventilation followed by breath retention and deep inhalations and exhalations), b) followed by exposure to cold (e.g. whole body exposure to ice-cold water or walking in cold environment bare-chested) and c) mindful body awareness focus on deep breathing (Kox et al., 2014). The Iceman is the world-record holder in several cold challenges, such as the fastest half-marathon on snow and ice while barefoot, and the longest duration while fully immersed in crushed ice (1 h and 50 min). Practice of the WHM appears to allow him to regulate his autonomic NS in the presence of severe cold. For example, a recent case study demonstrated that he could control his autonomic stress response during endotoxemia (Kox et al., 2014), indicating the ability of this method to modulate the innate immune response. Pertinent to our investigation, practice of the WHM has endowed the Iceman with remarkable tonic propensity for thermoregulatory defense. This endowment, and his putative brain and body responses to cold exposure must be reconciled and compared with recent in vivo studies in typical volunteers.

Recent studies have begun to detail functional MRI (fMRI) estimated response in CNS pathways to experimentally induced changes in body temperature (Muzik and Diwadkar, 2016). These studies have shown that controlled whole body cold exposure drives responses of homeostatic nuclei within the brainstem that mediate autonomic CNS responses to peripheral inputs (Satinoff, 1978). Additional naturalistic studies of endogenous thermoregulatory events have identified contributions from higher-order cortical areas such as the insular cortex, the anterior cingulate, the posterior parietal somatosensory cortex, and especially the orbitofrontal cortex. These regions collectively constitute networks for the interoception of the body's internal states and a value-generating network that guides behavior (Craig, 2002; Diwadkar et al., 2014). These “higher order” regions have a marginal (if any) modulatory effect on the autonomic NS, with no known direct anatomical pathways that can sub-serve interaction. However, anecdotal evidence suggests that top-down regulation might assume a much larger role in the autonomic regulatory cascade as previously assumed, even though these mechanisms remain subject to more systematic discovery.

His unique abilities make the Iceman an important specimen that allows investigation of highly adapted human thermoregulatory mechanisms, having provided important insights into physiology (Kox et al., 2012, 2014). Yet, imaging-driven insights into processes in the CNS and the periphery are either absent (brain) or limited (body) (Vosselman et al., 2014). In light of the above considerations, our study was designed to study the relationship between conscious and autonomic aspects of CNS function (represented in cortical and sub-cortical regions), and their comparative effects relative to the periphery during an oscillating cold thermal challenge. Imaging data obtained for the Iceman was compared to data acquired under identical challenges in a group of controls. By exploring CNS responses to cold exposure in this unique individual relative to a normative population, our objective was to discover the underlying correlates of cold resilience in the brain and body. The strength of this approach is that it relates the interpretation of the fMRI data (acquired in the CNS) to a specific physiological context (acquired in the periphery using PET imaging). Our results indicate that while his body's responses to our applied thermal stressor (in terms of activated brown adipose tissue) was relatively unremarkable, his brain showed substantially different functional responses during thermoregulatory challenge.

Material and methods

Subjects

The Human Investigation Committee of Wayne State University authorized the study and informed written consent was obtained from all participants. Study participants were screened for medical history and metabolic status, as assessed on the basis of routine laboratory tests and measured blood pressure. The Iceman and controls underwent a well-established research protocol established in our Imaging Center (Muzik et al., 2017) (see Table 1). For all participants body mass index (BMI) was calculated as weight/height2 (kg/m^2), and percent body fat (%) was calculated from the sum of skinfold measurements at the biceps, triceps, subscapular and suprailiac sites using Lange calipers. The lean body mass (LBM; kg) was subsequently calculated as body weight less fat mass. Although the control group was significantly younger than the Iceman, the rate-pressure product (representing myocardial workload which is directly related to hemodynamic response) was similar.

Study design

To assess functional brain responses to cold stress, the “Iceman” underwent a fMRI paradigm on two separate days. On each day, the fMRI paradigm consisted of an oscillating whole body temperature challenge designed to generate periods of mild hypothermia interspersed by periods of return to basal core body temperature (see below). The Day 1 acquisition was in a pre-scan “passive” state. The Day 2 acquisition followed the pre-scan practice of the WHM. The neuroimaging studies were complemented by scans of the periphery. Thus, on a third day the Iceman underwent a whole-body PET/CT imaging session using the tracers C11-hydroxyephedrine (HED) and 18F-fluorodeoxyglucose (FDG) during both thermoneutral (rest) and mild cold conditions also in a “passive” state. He was specifically instructed to not use the WHM prior or during the entire PET/CT protocol to allow assessment of peripheral tissue response to sympathetic activation during a baseline “passive” condition. This PET/CT protocol has been used in our Imaging Center in the past to study the effects of sympathetic stimulation on cold-induced activation of brown adipose tissue (BAT) (Muzik et al., 2012, 2013). During the protocol, whole body changes in daily energy expenditure (DEE, kcal/day) between the cold and thermoneutral conditions were assessed using indirect calorimetry and related to changes in PET tracer accumulation (HED and FDG). By definition, our typical controls having not been trained in the WHM, thus all fMRI and PET data in the control group was obtained in a “passive” state.

Mild cold exposure during both PET and fMRI acquisitions was

Table 1
Descriptive Statistics for the Iceman and the Control group.

Parameter	Iceman	Controls	range [min – max]
Subjects		20 (10 F/10 M)	
Age (years)	57	23.3 ± 3.8	19–32[a]
Height (cm)	182	172 ± 12	152–198
Weight (kg)	86	69 ± 16	53–101
BMI (kg/m^2)	25.9	23.0 ± 2.6	19.6–26.9
Body Fat (%)	28	25.4 ± 5.8	16–32
LBM (kg)	61.9	54.5 ± 14.5	38.8–84.7
RPP (min mmHg)	7191	7572 ± 1273	9325 - 4826

[a] Significant at the 0.05 level; RPP: rate-pressure product.